REMARKS

I. Status of the Application

Claims 1-6 and 8-16 are pending in the application. Claim 7 was cancelled in the preliminary amendment filed with the instant application on October 28, 2003. In the instant Office Action, claims 1, 2 and 5-11 stand rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Claims 1, 15 and 16 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 15 and 16 are rejected under 35 U.S.C. § 101, as being an improper definition of a process claim. Claims 1-14 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over McGinity et al., U.S. Patent No. 5,288,502, in view of Subramaniam et al., U.S. Patent No. 5,874,029, and further in view of Goedemoed et al., U.S. Patent No. 5,980,948. Claims 13, 14, 23 and 28 have been cancelled without prejudice to the filing of any appropriate continuation applications.

Applicants have amended the claims to more clearly define and distinctly characterize Applicants' novel invention. Claim 1 was amended to clarify the claim language. Support for claim 1 can be found at least in claim 1 as originally filed; at page 13, lines 22-23 of the specification, where Applicants teach a first solvent immiscible with water; at page 13, lines 24-25 of the specification, where Applicants teach a first solvent miscible with a second solvent; at page 13, lines 23-24 of the specification, where Applicants teach a polymer soluble in a first solvent; and at page 13, lines 24-25, where Applicants teach a polymer that is not soluble in a second solvent. Claim 9 was amended to clarify the claim language. Claims 15 and 16 were amended to recite a process. The amendments add no new matter.

Applicants respectfully request entry and consideration of the foregoing remarks, which are intended to place this case in condition for allowance.

II. Claims 1, 2, 5, 6 and 8-11 Are Enabled

At page 2, paragraph 2 of the instant Office Action, claims 1, 2 and 5-11 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner is of the opinion that claim 1 includes all polymers, but that the specification provides support for only one type of copolymer. The Examiner concludes that the specification does not enable any person skilled in the art to which it pertains, or with which it is most closely connected, to make or use the claimed invention commensurate in scope with the claim. Applicants respectfully traverse this rejection.

35 U.S.C. § 112, first paragraph requires that the specification must enable a person skilled in the art to make and use the claimed invention. However, a specification need not, and should not, disclose what is well known in the art. The invention that one skilled in the art must be enabled to make and use is that defined by the claims of the particular application. The issue of adequate enablement depends on whether one skilled in the art could practice the claimed invention without undue experimentation. Enablement is not precluded by the necessity of some experimentation such as routine screening, ***even if it is extensive routine screening***. Also, the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (MPEP 2164.01) if the level of skill in the art is high ***or if all of the methods needed to practice the claimed invention are well known***. *In re Wands*, 8 U.S.P.Q. 2d 1400, 1406 (Fed. Cir. 1988).

> The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. (Citations omitted). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands*, 8 U.S.P.Q. 2d at 1404.

Applicants' claimed invention is directed to a process for preparing an implant for controlled release of a bioactive agent *in vivo* comprising a polymer fiber loaded with one or more bioactive agents. Applicants respectfully submit that the instant specification provides ample direction and guidance to enable one of skill in the art to make and use the claimed invention. Applicants' example teaching the preparation of a polyethylene glycol terephthalate/polybutylene terephthalate copolymer is illustrative of a ***general method*** that can be used with any suitable polymers (page 5, lines 16-20). Thus, one of skill in the art could use a variety of polymers with this general method to arrive at the claimed invention. Applicants teach a variety of polymers that are suitable for use in the claimed invention (page 3, lines 11-12). For instance, Applicants teach that polymers such as polyalkylene glycols terephthalates and aromatic polyesters are appropriate for use in the claimed processes (page 4, lines 1-2). Applicants teach that suitable polyalkylene glycols terephthalates include, for example, polyethylene glycol terephthalate, polypropylene glycol terephthalate, polybutylene glycol terephthalate, and poloxamers (page 5, lines 28-31). Suitable polyesters include, for example, polyethylene terephthalate, polypropylene terephthalate, and polybutylene terephthalate (page 5, lines 13-15). Applicants teach a suitable molecular weights for polymers, as well as methods for determining molecular weights (page 4, lines 7-23).

Furthermore, the references cited by the Examiner illustrate that, at the time of filing, a variety of polymers for use with bioactive agents were known. For example, Goedemoed et al. teaches drug delivery matrices comprising a variety of polyetherester copolymer compounds consisting of various structural formulas (columns 1-7). McGinity et al. teaches the use of PLA and PLGA combined with biological agents (example 1). Subramaniam et al. teaches microparticles and nanoparticles comprising pharmaceutical compositions and poly(D,L-lactide-

glycolide) copolymer (column 5, lines 23-26; examples 1-4). Thus, suitable polymers were known to those of skill in the art at the time of filing.

Additionally, the Examiner acknowledges that "the state of the art in ***preparing polymers carrying drugs*** is ***well defined in the art*** and the process in the instant claims are considered ***conventional***" and that "it is ***highly likely*** that one can ***successfully make*** drug delivery agents by ***mixing a polymer solution*** with a solution of drug or bioactive agent dissolved in appropriate solvent," (page 3 parts (b) and (d), emphasis added).

The Examiner asserts that given the broadest interpretation, the claim for the process for preparing a polymer loaded with bioactive agents contemplates the use of all polymers, but that "only one working example is disclosed in the specification in which the PEGT/PBT copolymer is used." The Examiner then concludes "[t]herefore contrary to the claims, applicant process of making polymer loaded with bioactive agents is enabled only when PEGT/PBT polymer forms the matrix." Applicants respectfully disagree. The Examiner's basis for the enablement rejection is that "***only one working example*** is disclosed in the specification in which the PEGT/PBT copolymer is used" (emphasis added). Applicants respectfully submit that ***all*** of the Wands factors should be considered when making a determination of enablement and that it is ***not proper*** to base non-enablement solely based on ***one factor***.

> It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis ***must consider all of the evidence*** related to each of the factors, and any conclusion of nonenablement must be based on the evidence as a whole. MPEP §2164.01(a) citing *In re Wands* at 737, 740, emphasis added.

Furthermore, Applicants respectfully submit that they need not provide more than one working example to enable the invention: "the presence of one working example should ***never be the sole reason for rejecting claims*** as being broader than the enabling disclosure, even though it

is a factor to be considered with all the other factors" (MPEP §2164.02, emphasis added). The MPEP states "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does ***not turn on whether an example is disclosed***" (§2164.02, emphasis added). Furthermore, "[t]he specification need not contain an example if the invention is ***otherwise disclosed*** in such manner that one skilled in the art will be able to practice it ***without an undue amount of experimentation***" (MPEP §2164.02, citing *In re Borkowski*, 422 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956), emphasis added). As set forth above, Applicants adequately describe how to make and use the claimed invention without undue experimentation and that a variety of polymers that are combinable with biological agents were well known in the art at the time of filing. At page 3 of the instant Office Action, the Examiner has confirmed at least this from reading the specification. Accordingly, one of skill in the art could arrive at the claimed invention without undue experimentation.

At page 3 of the instant Office Action, the Examiner states that "the relative skill of those practicing the art making drug delivery agents and devices carrying drugs wherein the agents or devices are made of polymers is not high in that any person with minimum education can make the polymeric drug delivery agents and incorporate drugs in said agents." Applicants respectfully disagree with the Examiner's assertion that the level of skill in the art of polymer implants is low. Applicants respectfully submit that the "hypothetical person having 'ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of ***understanding the scientific and engineering principles*** applicable to the art" MPEP §2141.03, citing *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394, emphasis added. Applicants respectfully submit that the person of ordinary skill in the art of polymer implants is ***not*** a "person with minimum education," as asserted by the Examiner, since such a person would

not understand the scientific and engineering principles with respect to polymer implants. Instead, a person of ordinary skill in the art of polymer research includes Ph.D. level scientists. This is underscored by the fact that Bala Subramanian, Said Saim, Roger Rajewski, Valentino Stella, and James McGinity, inventors listed on the face of McGinity et al. (U.S. Patent No. 5,288,502) or Subramaniam et al. (U.S. Patent No. 5,874,029) (both cited by the Examiner), all have Ph.D. degrees (highlighted in Attachment A). Ph.D. level and even Masters level researchers would not be "burdened with undue painstaking experimentation study in order to determine the suitability of all types of polymers for use in the process" as asserted by the Examiner, and would instead easily be able to practice the claimed invention using the teachings provided by Applicants' instant specification.

For at least these reasons, Applicants' specification enables a person of skill in the art to make and/or use the claimed invention. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 2, 5, 6 and 8-11 under 35 U.S.C. § 112, first paragraph.

III. Claims 1, 15 and 16 Are Definite

At page 4, paragraph 3 and page 5, paragraph 4 of the instant Office Action, claims 1, 15 and 16 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner asserts that in claim 1, there is insufficient antecedent basis for the limitation "allowing the first solvent to migrate into the second solvent to obtain a solid, fibrous polymer loaded with bioactive agent; i.e. step (d)" because the first solvent in step (a) of the

process is already consumed when it is mixed with the bioactive agent solution, and that referring back to the first solution makes the steps indefinite. The Examiner states that Applicants may overcome the indefiniteness claim by specifying the source of the oil and eliminating the reference to the first solvent as this is consumed in step (b).

At the outset, Applicants respectfully point out that the claim language the Examiner recites is from claim 1 as originally filed, and that Applicants submitted a preliminary amendment with the instant continuation application filed on October 28, 2003. A copy of the previously filed preliminary amendment is submitted herewith. Claim 1 set forth in the preliminary amendment recites in relevant part: (a) providing a solution of the polymer in a first solvent immiscible with water; (b) adding an aqueous solution of the bioactive agent to the polymer solution to form an emulsion; (c) immersing the emulsion in a second solvent miscible with the first solvent, and in which the polymer insoluble by injecting the emulsion through a nozzle into the second solvent; and (d) allowing the first solvent to migrate into the second solvent to form a solid-polymer fiber loaded with the bioactive agent.

Presently pending claim 1 does not recite the term "oil." Accordingly, Applicants submit that it is unnecessary to refer to a source of oil to render the claim definite. Further, Applicants respectfully submit that the first solvent is not "already consumed when it is mixed with the bioactive agent solution" as asserted by the Examiner. An emulsion is defined as "a system (as fat in milk) consisting of a liquid dispersed...in an immiscible liquid usu. droplets larger than colloidal size" (Merriam-Webster's Collegiate Dictionary definition, set forth as Attachment B). Thus, an emulsion comprises a liquid portion and an immiscible liquid portion. Forming an emulsion does not consume the solvent because it is still present. Accordingly, the solvent is available for use in step (e). Thus, Applicants respectfully submit that the claims are definite.

The Examiner further asserts that claim 1 is indefinite with respect to oil in water. The Examiner queries whether the source of the oil is the first solution or the bioactive solution. Applicants respectfully submit that claim 1 does not recite "water-in-oil" but instead recites "adding an aqueous solution of the bioactive agent to the polymer solution to form an emulsion". Applicants submit that this rejection is moot in view of the presently pending claims and request that this rejection be withdrawn.

The Examiner asserts that claims 15 and 16 are indefinite for merely reciting a use without any active, positive steps delimiting how the use is actually practiced. The Examiner further rejects claims 15 and 16 under 35 U.S.C. §101 for being an improper definition of a process. Without acquiescing to these rejections, Applicants respectfully submit that claim 15 has been amended to recite "process according to claim 1, wherein the implant is" and to remove "use" language. Similarly, claim 16 was amended to recite "process according to claim 13, wherein the" and to remove "use" language. Accordingly, Applicants respectfully request that the rejections of claims 15 and 16 be reconsidered and withdrawn.

IV. Claims 1-6 and 8-14 Are Nonobvious over the Cited Art

At page 6, paragraph 2 of the instant Office Action, claims 1-14 stand rejected under 35 U.S.C. §103(a) as being unpatentable over McGinity et al., U.S. Patent No. 5,288,502, in view of Subramaniam et al., U.S. Patent No. 5,874,029, further in view of Goedemoed et al., U.S. Patent No. 5,980,948. The Examiner is of the opinion that Applicants' invention as a whole would have been *prima facie* obvious to one of ordinary skill at the time the invention was made.

Applicants respectfully traverse this rejection. Applicants respectfully submit that to establish *prima facie* obviousness of a claimed invention, each and every claim limitation must

be taught or suggested by the prior art. The cited references, alone or in combination, fail to teach or suggest each and every element of the claimed invention. The Examiner is of the opinion that Applicants' claims are drawn to "a process of preparing a polymer loaded with one or more bioactive agents." Applicants respectfully reiterate that the claim language the Examiner recites is from claim 1 as originally filed, and that Applicants submitted a preliminary amendment with the instant continuation application filed on October 28, 2003. In the preliminary amendment, claim 1 was amended to recite a process for preparing an implant for controlled release of a bioactive agent *in vivo* comprising a polymer fiber loaded with one or more bioactive agents, said process comprising a ***wet spinning technique***.

Applicants' claimed invention is based on the novel discovery of a process using mild conditions to produce polymer fibers that have a controlled rate of release of bioactive agent. Because the claimed wet spinning technique is carried out under mild conditions, the functional integrity of bioactive agents used in the process can be maintained (page 2, lines 7-19). Applicants have also discovered that the release rate of the bioactive agent from the polymer can be manipulated by modifying the water content used during wet spinning (page 19; Figure 3).

Applicants' claimed process yields polymer fibers that can be used inside the body and are useful for a variety of biological, pharmaceutical and surgical applications in which controlled release of a bioactive substance is desired (page 16, lines 9-12). For example, the claimed implants are useful for the release of bioactive agents inside an animal or human body, and can be used as scaffolds for tissue engineering in order to replace or repair tissues (page 3, lines 4-17 and page 16, lines 8-14 of the specification). Accordingly, the claimed implants are valuable for use in a variety of applications such as in surgical devices and aids, for treating infections, and for preventing unwanted pregnancies.

The cited references fail to teach or suggest each and every element of the claimed invention. McGinity et al. is directed to the preparation of multi-phase polymeric microspheres using a multiple emulsion solvent technique (abstract; column 15, line 19 to column 16, line 22). McGinity et al. neither teaches nor suggests a polymer fiber, as claimed by Applicants. McGinity et al. also fails to teach or suggest a process comprising a wet spinning technique, as claimed by Applicants. In addition, McGinity et al. fails to teach or suggest an implant as claimed by Applicants. Accordingly, McGinity et al. fails to teach or suggest the claimed invention.

Subramaniam et al. fails to cure the deficiencies of McGinity et al. Subramaniam et al. is directed to the production of microparticles and nanoparticles by atomization (column 5, lines 23-52). Subramaniam et al. fails to teach or suggest a process comprising a wet spinning technique, as claimed by Applicants. Accordingly, the combination of Subramaniam et al. and McGinity et al. fails to teach or suggest the claimed invention.

Goedemoed et al. fails to cure the deficiencies of the primary references. Goedemoed et al. is directed to drug delivery matrices made by solvent evaporation or by spray-drying (column 1, lines 4-10; column 16, lines 11-13). Nowhere does Goedemoed et al. teach the claimed process comprising a wet spinning technique. Furthermore, Goedemoed et al. fails to teach the claimed implants.

Thus, the combination of references fails to teach each and every element of the claimed invention. Accordingly, Applicants respectfully request that rejection of claims 1-6 and 8-14 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

V. Conclusion

Having addressed all outstanding issues, Applicants respectfully request reconsideration and allowance of the case. To the extent the Examiner believes that it would facilitate allowance of the case, the Examiner is requested to telephone the undersigned at the number below.

Respectfully submitted,

Dated: February 8, 2005

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	
	)	
Jeroen Mattijs Bezemer,	)	Examiner:
Clemens Antoni van Blitterswijk,	)	
Jan Feijen, and Dirk Wybe Grijpma	)	
	)	
Serial No.: TBA (Cont. of USSN 09/676,648)	)	Art Unit:
	)	
Filed: Herewith	)	
	)	
Title: POLYMERS WITH BIOACTIVE AGENTS	)	

Commissioner for Patents
Mail Stop Patent Application
P.O. Box 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Dear Sir:

Preliminary to examination, please enter the following amendments in the above-referenced continuation application being submitted herewith.

Amendments to the Specification:

At page one, after the title and before the first sentence, please insert the following paragraph:

--RELATED APPLICATIONS

This application is a continuation of U.S. Patent Application Serial No. 09/676,648, filed on September 29, 2000; which claims priority from European Patent Application No. EP 99203195.5, filed on September 30, 1999; both which are hereby incorporated herein by reference.--

At page one, before line 1 and after the above-inserted paragraph entitled "Related Applications," please insert the following subheadings:

-- BACKGROUND OF THE INVENTION

1. Field of the Invention --

At page one, between lines 4 and 5 insert --

2. Description of the Related Art --

At page two, between lines 17 and 18, insert --

SUMMARY OF THE INVENTION --

At page two, between lines 28 and 29, insert the following:

-- BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B depict scanning electron micrographs of a cross-section of protein loaded PEG/PBT fibers. (A) depicts 500x magnification and (B) depicts 2000x magnification.

Figures 2A-2D depict scanning electron micrographs of the structure of structure of protein loaded PEG/PBT fiber meshes. (A) and (C) depict cross sections. (B) and (D) depict surface morphology.

Figure 3 graphically depicts the total protein release from bonded fiber meshes.

DETAILED DESCRIPTION OF THE INVENTION --

Listing of the Claims:

1. (Currently Amended) A process for preparing an implant for controlled release of a bioactive agent *in vivo* comprising a polymer fiber loaded with one or more bioactive agents, said process comprising a wet spinning technique having the steps of:

a) providing a solution of the polymer in a ~~suitable~~ first solvent immiscible with water;

b) adding an aqueous solution of the bioactive agent to the polymer solution to ~~obtain a water-in-oil~~ form an emulsion;

c) immersing the ~~water-in-oil~~ emulsion in a ~~suitable~~ second solvent miscible with the first solvent, and in which the polymer is essentially miscible by injecting the emulsion through a nozzle into the second solvent; ~~and~~

d) allowing the first solvent to migrate into the second solvent to ~~obtain~~ form a solid~~,~~ ~~fibrous~~ polymer fiber loaded with the bioactive agent, wherein water content of the aqueous solution in step (b) affects a rate of release of the bioactive agent *in vivo*; and

e) shaping the polymer fiber into an implant.

2. (Currently Amended) ~~A~~ The process according to claim 1, wherein the polymer is biocompatible and biodegradable.

3. (Currently Amended) ~~A~~ The process according to claim 2, wherein the polymer is an amphiphilic block copolymer, comprising hydrophilic blocks and hydrophobic blocks.

4. (Currently Amended) ~~A~~ The process according to claim 3, wherein the polymer is a copolymer comprising a polyalkylene glycol and an aromatic ester.

5. (Currently Amended) ~~A~~ The process according to claim 1, wherein the bioactive agent is ~~chosen~~ selected from the group consisting of antimicrobial agents, ~~such as antibacterial and~~ anti-viral agents, anti-tumor agents, immunogenic agents, lipids, lipopolysaccharides, hormones and growth factors.

6. (Currently Amended) ~~A~~ The process according to claim 1, wherein the bioactive agent is ~~chosen~~ selected from the group consisting of peptides, oligopeptides, polypeptides and proteins.

7. (Canceled)

8. (Currently Amended) ~~A~~ The process according to claim ~~7~~ 1, wherein the first solvent has a greater solubility in the second solvent when the polymer is dissolved in the first solvent.

9. (Currently Amended) ~~A~~ The process according to claim 1, wherein the ~~water-in-oil~~ emulsion is immersed into the second solvent by injecting through a nozzle, a syringe or an extruder.

10. (Currently Amended) A ~~bioactive agent~~ polymer loaded ~~polymer obtainable by the method of~~ with one or more bioactive agents according to claim 1.

11. (Currently Amended) A ~~bioactive agent~~ polymer loaded ~~polymer obtainable by a process according~~ with one or more bioactive agents according to claim 9.

12. (Currently Amended) A bioactive agent loaded polymer according to claim 10, wherein said bioactive agent is a peptide, oligopeptide, polypeptide or protein.

13. (Original) A process for bonding fibers according to claim 1 to form a fibrous mesh, wherein the fibers are collected and are bonded together by use of a suitable solvent mixture.

14. (Original) A fibrous mesh obtainable by a process according to claim 13.

15. (Original) The use of a bioactive agent loaded polymer, according to claim 10, as a carrier for controlled drug release or as a scaffold for tissue engineering.

16. (Original) The use of a fibrous mesh according to claim 14 as a carrier for controlled drug release or as a scaffold for tissue engineering.

REMARKS

Prior to the calculation of the filing fee, Applicants respectfully request entry of the above amendments. The Commissioner is hereby authorized to charge any additional fees or credit overpayment to Deposit Account No. 19-0733.

Respectfully submitted,

Dated: October 28, 2003

By _____

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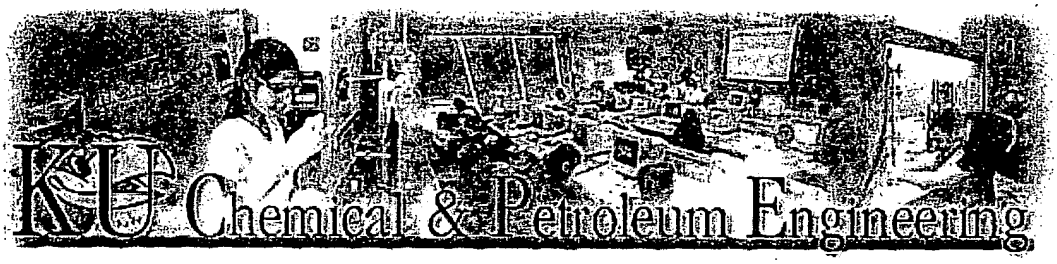

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M.S., Chemical Engineering, University of Notre Dame
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Center for Environmentally Beneficial Catalysis receives National Science Foundation Engineering Research Center Award

Research Interests

Environmentally Beneficial Catalysis and Reaction Engineerin Near-critical Processing, Mathematical Modeling.

Exploiting Supercritical Fluids in Heterogeneous Catalysis

During the last decade, supercritical fluids (such as supercritical carbon dioxide and supercritical water) have been increasingly explored for performing a variety of catalytic reactions such as hydrogenations, alkylations, aminations and oxidations, to menti a few.

Adsorption/desorption and pore-transport are key parameters influencing the activity, effectiveness factors and product

selectivity in porous catalysts. With conventional reaction media (either gas or liquid phase), one of these parameters is generally favorable while the other is not. For instance, while desorption of heavy hydrocarbons from the catalyst is usually the rate-limiting step (and therefore detrimental to catalyst performance) in gas-phase reactions, transport of the reactants/products is the limitin step in liquid-phase reaction media. Furthermore, with conventional media, it is usually difficult to achieve the desired combination of fluid properties for optimum system performance. In contrast, density and transport properties can be continuously pressure-tuned in the near-critical (*nc*) region to obtain unique fluid properties (e.g., gas-like transport properties, liquid-like solvent power and heat capacities), that offer several advantage such as these:

- the *in situ* extraction of heavy hydrocarbons (i.e., coke precursors) from the catalyst surface *and* their transport out the pores before they are transformed to consolidated coke, thereby extending catalyst lifetime;
- complete miscibility of reactants such as hydrogen in the reaction mixture and enhanced pore-transport of these react to the catalyst surface, thereby promoting desired reaction pathways;
- enhanced desorption of primary products, thereby preventin secondary reactions that adversely affect product selectivity; and
- control of temperature rise in exothermic reactions, thereby preventing "reactor runaway" conditions.

Experimental and theoretical investigations are underway to demonstrate pressure-tuning effects on catalyst activity and product selectivity during continuous processing of a variety of reactions such as these: geometric isomerization and alkylation solid acid catalysts; Fischer-Tropsch synthesis on supported Fe catalysts; and fixed-bed hydrogenation on supported catalysts. The possibility to use dense phase CO_2 as replacement for conventional solvents, to create compressible reaction mixtures perform solid acid catalysis with extended activity (an environmentally safer alternative to liquid acid processes) and fixed-bed hydrogenations with tunable selectivity and controlled temperature rise (preferred over slurry phase operation) makes r reaction media particularly appealing alternatives to conventiona reactor operation.

Catalytic Oxidations in Dense Carbon Dioxide-Based Reacti

***Media* (with Professor Daryle Busch of the Department of Chemistry, University of Kansas)**

This research program seeks a complete understanding and ultimate exploitation of homogenous catalytic oxidation chemistry in dense phases of carbon dioxide. A major advance and the focus of current research is the discovery and demonstration, in these laboratories, that CO_2-expanded solvents are highly desirable media for homogeneous catalytic oxidations. The research program exploits these unique media and a successful perspective on catalyst design to develop new environmentally benign homogeneous transition metal catalyzed oxidation systen for such chemical reactions as olefin epoxidation, functional grou oxidation, and bleach.

The new medium, CO_2-expanded solvent, is produced by increasing the volume of the solvent (that is soluble in CO_2) through the addition of relatively large amounts of CO_2. Each CO_2-expandable solvent can, in principle, generate a continuum of media ranging from the neat organic solvent to neat CO_2. Thu the solvent properties may be varied to accommodate contrastin solubilities simultaneously, like those of oxygen and catalysts based on metallic elements; a large amount of CO_2 favors oxyge solubility and polar organic solvents favor metal catalyst solubilit We have demonstrated that the beneficial physical properties ma be elegantly combined in CO_2-expanded reaction mixtures to perform a variety of homogeneous catalytic oxidations. *Reaction advantages* are:

- Higher oxygen miscibility (up to two orders of magnitude) compared to organic solvents.
- Applicability to transition metal catalysts without ligand modification (e.g. no environmentally non-benign fluorination enhance their solubilities).
- Between one to two orders of magnitude greater TOFs and either comparable or better product selectivities than in neat organic solvent or *sc*CO_2.
- Following the reaction cycle, the catalyst may be separated f the reaction mixture by simply adding more CO_2. The catalys free reaction mixture may then be subjected to stepwise pressure reduction to effect the separation of product(s) and remaining reactants.

Environmental and economic advantages include the following:

- Substantial (up to 80 vol.%) replacement of organic solvents with dense-phase CO_2,
- Milder process pressure (tens of bars) compared to *sc*CO_2 (hundreds of bars),
- With substantial CO_2 expansion, explosive mixtures can be avoided in the presence of oxygen and other potent oxidants Thus, oxidation in CO_2-expanded solvents is inherently safer than in traditional solvents.
- Enhanced reaction rates and low process pressures give favorable process economics.

Our current foci include: (1) the iterative optimization by molecul design of known and new homogeneous catalyst systems for oxidations in dense phase CO_2 media; (2) the incorporation and evaluation of outstanding catalysts in aqueous or other media th may become co-solvents, intravesicular solvents, or otherwise partnered with dense phase CO_2; and (3) Modeling of CO_2-expanded solvent media complemented by detailed mechanistic studies of selected catalytic reactions.

Pharmaceutical Processing with Dense Phase Carbon Dioxi

Replacement of traditional solvents with *sc* carbon dioxide (because of its pressure-tunable physical/transport properties an environmentally-benign nature) is receiving increased attention i pharmaceutical processing. Among the applications, particle micronization (to increase drug bioavailability) and coating of dru compounds (for both aesthetic as well as functional reasons) using *sc* carbon dioxide as the processing medium hold promise for large-scale application.

Spray processes employing *sc* CO_2 (P_c = 72.8 atm; T_c = 31.1°C) as an anti-solvent are well known. In this method, the solute is solubilized in an organic solvent. The solution is then sprayed int a chamber containing sc-CO_2, which selectively solubilizes the solvent from the spray droplets, causing the solute to precipitate as microparticles. In an ongoing joint research effort with the Center for Drug Delivery Research at the University of Kansas, investigations are underway aimed at a fundamental understanding of how process variables (such as nozzle design, spray solution rate, antisolvent flow rate, etc.) affect particle size distribution, crystallinity, bioactivity, etc. Such an understanding i essential for rational design and scale-up of this promising technology in pharmaceutical practice.

In a parallel effort, we have developed a continuous coating process in which the drug-laden solution is sprayed on beads or tablets (coating substrates) suspended in *sc* CO_2. The *sc* CO_2 also acts as an antisolvent for the drug selectively solubilizing the solvent from the spray droplets. The resulting drug particles are deposited (i.e., coated) on the substrate. Using this technique, we have successfully coated glass, non-pareil sugar and alumina beads with polymers (such as ethyl-cellulose and PLGA copolymer) and drugs (such as hydrocortisone). This process complements the conventional Wurster coater, expanding the range of substrate-drug combinations. Our goal is to develop a fundamental understanding of the effects of operating parameter such as pressure, temperature and spray-rates on coating morphology and uniformity. Such an understanding is essential for rationally developing coating applications of interest to the pharmaceutical industry.

Links to Research Group(s)

Bala's Research Group

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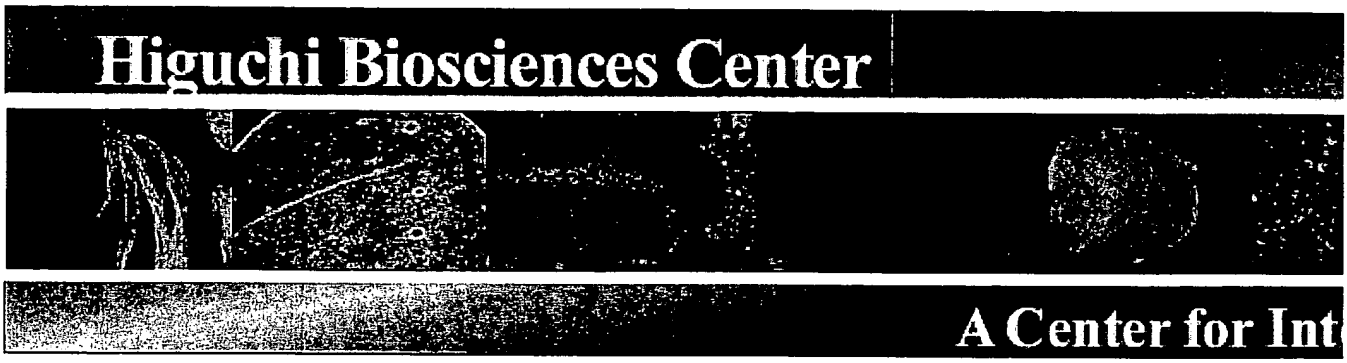

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Education

- Ph.D., Pharmaceutical Chemistry, Advisor: Valentino J. Stella, Universit of Kansas, 1990
- M.S., Pharmaceutical Chemistry, Graduate Adviser: Valentino J. Stella, University of Kansas, 1987
- B.S., Chemistry and Biochemistry, University of Kansas, 1984

Research Interests

- Development of novel drug delivery technologies including their pharma evaluation
- Application of physical and chemical means to address pharmaceutical p biological evaluation, and regulatory approval of medicinal agents
- Focus on agents and technologies for parenteral administration, includi development, lyophilization cycle development, novel processing techno cell-specific drug targeting technologies

Economic Development Experience

In the positions of Assistant Director, Associate Director, and currently, Acting Direct Drug Delivery Research (CDDR), I have been involved in the Kansas Technology Ente development of University of Kansas technologies for potential commercialization in t has supported the continued development and patent prosecution for the sulfobutyl e been patented by the University and licensed to CyDex, Inc., of Overland Park, KS. Cy under the trade name "Captisol" for use as solubilizing and stabilizing agents in the fo

During my tenure at CDDR I have helped guide the development of two additional tec

supercritical fluids and novel prodrug technologies. Multiple patents in both these are
University to CritiTech, Inc., and the prodrug technologies have been licensed to ProQ
Lawrence, KS. Both of these companies are in the early stages of development and the
continuing to be advanced within CDDR. I have been involved in the incorporation of
reviewing the license arrangements, participated in making presentations to financing
contributed to the business plan development and multiple grant preparation activitie
technical consultants. In addition, CDDR has provided technical input for three Kansa
University.

Representative Publications

V. Zia, R.A. Rajewski and V.J. Stella, Effect of cyclodextrin charge on complexation of comparison of (SBE)7M-beta-CD to HP-beta-CD, *Pharm. Res.*, 18(5): 667-673 (2001).

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V. Stella, R. Rajewski, V. Rao, J. McGinity, G. Mosher; Sulfoalkyl ether cyclodextrin b
pharmaceutical formulations; U.S. Patent 6,046,177.

V. Stella, R. Rajewski, J. McGinity; Sulfoalkyl ether cyclodextrin based solid pharmac
Patent 5,874,418.

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Faculty Report

THE UNIVERSITY OF KANSAS MEDICAL CENTER

Vol. 15 No. 27 July 8, 1996

Sections of this page:

News from the School of Medicine-Kansas City and Wichita

The **medical faculty council** will meet at 7:30 a.m. July 16 in 2004 Orr-Major at the Kansas City campus and in the Great Plains Room at the Wichita campus.

News from the School of Medicine-Kansas City

Sumedha Panchal, MD, has been named director of obstetrical anesthesia and an assistant professor of anesthesiology, effective July 1, 1996. She will devote most of her clinical efforts to the anesthetic management of obstetric and gynecologic surgery patients. She received her bachelor's degree cum laude in biochemistry from **Kansas State University**, Manhattan. After she earned her medical degree from KU in 1990, she was an intern in internal medicine and then a resident in anesthesiology at **Northwestern University**, Chicago. In 1994 and 1995, she was a locum tenens anesthesiologist. She was a fellow in obstetric anesthesia in 1995 and 1996 at

Baylor College of Medicine, Houston.

John Doull, MD, PhD, professor emeritus of pharmacology, recently received an **honorary doctorate from the University of Kuopio** in Finland. KU Medical Center's department of pharmacology, toxicology and therapeutics has had a long-standing relationship with the University of Kuopio. Both universities have operated an exchange of faculty and students for more than 20 years. As a participant in this program, Doull, who joined KU Medical Center in 1967, has trained students and faculty from the University of Kuopio at KU Medical Center and given several lectures in Finland. Of the eight honorary doctorates bestowed on recipients from throughout the world, two are from the University of Kansas - Doull and **Valentino Stella**, PhD, professor of pharmaceutical chemistry and director of the Center for Drug Delivery Research at the KU Lawrence campus. They received their honors at a special convocation June 7 in Finland. **Thomas Pazdernik**, PhD, professor of pharmacology and toxicology at KU Medical Center, also attended the convocation and lectured on neurotoxicology at the University of Kuopio.

Carlos Dujovne, MD, professor of medicine and pharmacology and director of the Lipid and Arteriosclerosis Prevention Clinic, was a lecturer at the **VI World Congress of Cardiac Rehabilitation** on "Expanding Scope in the Next Century: Integration With New Management and Technologies" June 16-20 in Buenos Aires, Argentina. He presented "The Use of Antioxidants in the Treatment and Prevention of Arteriosclerosis" and "An Update on the Statins."

Joseph Lutkenhaus, PhD, professor of microbiology, molecular genetics and immunology, received a four-year, $830,171 direct costs grant from the **National Institutes of Health** for "Regulation of Expression of Cell Division Genes."

Dennis Allin, MD, director and assistant professor of emergency medical services, **Rodolfo Martinez-Ferrate**, second-year resident in family medicine, and Kathy Wright, RN, BSN, nurse analyst in nursing infomatics, gave presentations at the **Farm Injury Management Seminar** May 31-June 2 in Ulysess. The conference was sponsored by Grant County EMS in conjunction with the Southwest Kansas Area Health Education Center.

News from the School of Medicine-Wichita

Ronald Martin, MD, professor and chair of psychiatry and behavioral sciences, has been appointed chair of the **American Psychiatric Association's** committee on medical student education. He also has been elected deputy legislative representative for Area IV (Midwest region) of the organization.

News from the School of Allied Health

Khatab Hassanein, PhD, professor and chair of biometry, and **Ruth Hassanein**, PhD, professor of biometry, are among the co-authors of "Transmission of *Toxoplasma Gondii* in Panama City, Panama: A Five-Year Prospective Cohort Study of Children, Cats, Rodents, Birds and Soil," which was published in the *American Journal of Tropical Medicine and Hygiene*, Vol. 53, No. 5. The other authors are **Jacob Frenkel**, MD, former professor emeritus of pathology and laboratory medicine; **E. Brown**, Institut de Puericulture, Paris; and **P. Thulliez** and **R. Quintero-Nunez**, Ministerio de Salud, Gorgas Memorial Laboratory and Instituto de Seguro Social, Panama City, Panama.

As chair of the research development committee of the **American Occupational Therapy Foundation**, **Winnie Dunn**, PhD, OTR, FAOTA, professor and chair of occupational therapy education, attended the organization's research advisory council meeting in Seattle June 22-24.

Prepared by

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James W. McGinity, Ph.D.

James W. McGinity is Professor and Division Head of Pharmaceutics in the College of Pharmacy, The University of Texas at Austin. He received his Ph.D. in Physical Pharmacy in 1972 from the University of Iowa and joined the Squibb Institute for Medical Research as a research scientist until his appointment at University of Texas in 1976, where he now holds the Johnson and Johnson Centennial Chair in Pharmacy. Professor McGinity's research interests and publications are in the areas of Physical Pharmacy and Pharmaceutical Technology. He has been issued fifteen U.S. patents and currently has many others in review. His research emphasis is on novel drug delivery systems including solid dosage forms, microencapsulation, powder technology, transdermal systems and hot-melt extrusion. He has published in Science, Journal of Pharmaceutical Sciences, Pharmaceutical Development and Technology, Journal of controlled Release, Pharmaceutical International Journal of Pharmaceutics and Journal of Microencapsulation. During his tenure at the University of Texas, twenty-three Ph.D. students have graduated under his supervision. In addition, he has supervised thirty-one post-doctoral fellows and visiting scientists. Professor McGinity is USA Editor for the European

Volumes and Issues

2004
Vol. 5 No. 4
Vol. 5 No. 3
Vol. 5 No. 2
Vol. 5 No. 1

2003
Vol. 4 No. 4
Vol. 4 No. 3
Vol. 4 No. 2
Vol. 4 No. 1

2002
Vol. 3 No. 4
Vol. 3 No. 3
Vol. 3 No. 2
Vol. 3 No. 1

2001
Vol. 2 No. 4
Vol. 2 No. 3
Vol. 2 No. 2
Vol. 2 No. 1

2000
Vol. 1 No. 4
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Journal of Pharmaceutics and Biopharmaceutics and has been a consultant to the FDA and to many pharmaceutical and chemical companies both in the USA and Europe.

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Abb

em-ty-head-ed \-'he-dəd\ *adj* (1650) : SCATTERBRAINED

empty nest-er \-'nes-tər\ *n* (1962) : a parent whose children have grown and moved away from home

empty nest syndrome \em(p)-tē-'nest-\ *n* (1972) : the emotional letdown experienced by an empty nester

em-pur-ple \im-'pər-pəl\ *vb* **em·pur·pled; em·pur·pling** \-'pər-p(ə-)liŋ\ (1590) : to tinge or color purple ~ *vi* : to become purple

em-py-ema \,em-pī-'ē-mə\ *n, pl* **-ema·ta** \-mə-tə\ *or* **-emas** [LL, fr. Gk *empyēma*, fr. *empyein* to suppurate, fr. *em-* ²en- + *pyon* pus — more at POUT] (ca. 1605) : the presence of pus in a bodily cavity — **em·py·emic** \-mik\ *adj*

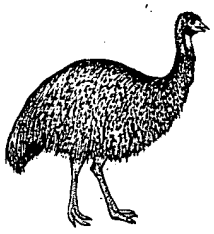
em-py-re-al \,em-pī-'rē-əl, -pə-; em-'pir-ē-əl, -'pī-rē-\ *adj* [LL *empyrius*, fr. LGk *empyrios*, fr. Gk *em-* ²en- + *pyr* fire] (15c) **1** : of or relating to the empyrean : CELESTIAL **2** : SUBLIME

em-py-re-an \-ən\ *adj* (15c) : EMPYREAL

empyrean *n* (ca. 1610) **1 a** : the highest heaven or heavenly sphere in ancient and medieval cosmology usu. consisting of fire or light **b** : the true and ultimate heavenly paradise **2** : FIRMAMENT, HEAVENS **3** : an ideal place or state

EMT \,ē-,em-'tē\ *n* [*e*mergency *m*edical *t*echnician] (1972) : a specially trained medical technician licensed to provide basic emergency services before and during transportation to a hospital — compare PARAMEDIC

emu \'ē-(,)myü, -mü\ *n* [modif. of Pg *ema*] (1656) **1** : any of various tall flightless birds (as the rhea) **2** : a swift-running Australian bird (*Dromaius novaehollandiae*) with undeveloped wings that is related to and smaller than the ostrich



emu 2

em-u-late \'em-yə-,lāt\ *vt* **-lat·ed; -lat·ing** [*aemulatus*, pp. of *aemulari*, fr. *aemulus* rivaling] (1582) **1 a** : to strive to equal or excel **b** : IMITATE; *esp* : to imitate by means of an emulator **2** : to equal or approach equality with

em-u-late \-lət\ *adj* (1602) *obs* : EMULOUS

em-u-la-tion \,em-yə-'lā-shən\ *n* (1542) **1** *obs* : ambitious or envious rivalry **2** : ambition or endeavor to equal or excel others (as in achievement) **3 a** : IMITATION **b** : the use of or technique of using an emulator — **em·u·la·tive** \'em-yə-,lā-tiv\ *adj* — **em·u·la·tive·ly** *adv*

em-u-la-tor \'em-yə-,lā-tər\ *n* (1589) **1** : one that emulates **2** : hardware or software that permits programs written for one computer to be run on another usu. newer computer

em-u-lous \'em-yə-ləs\ *adj* (1535) **1 a** : inspired by or deriving from a desire to emulate **b** : ambitious or eager to emulate **2** *obs* : JEALOUS — **em·u·lous·ly** *adv* — **em·u·lous·ness** *n*

emul·si·fi·er \i-'məl-sə-,fī(-ə)r\ *n* (1888) : one that emulsifies; *esp* : a surface-active agent (as a soap) promoting the formation and stabilization of an emulsion

emul·si·fy \-,fī\ *vt* **-fied; -fy·ing** (1859) : to disperse (as an oil) in an emulsion; *also* : to convert (two or more immiscible liquids) into an emulsion — **emul·si·fi·able** \i-'məl-sə-,fī-ə-bəl\ *adj* — **emul·si·fi·ca·tion** \i-,məl-sə-fə-'kā-shən\ *n*

emul·sion \i-'məl-shən\ *n* [NL *emulsion-, emulsio*, fr. L *emulgēre* to milk out, fr. *ex-* + *mulgēre* to milk; akin to OE *melcan* to milk, Gk *amelgein*] (1612) **1 a** : a system (as fat in milk) consisting of a liquid dispersed with or without an emulsifier in an immiscible liquid usu. in droplets of larger than colloidal size **b** : the state of such a system **2** : SUSPENSION 2b(3); *esp* : a suspension of a sensitive silver salt or a mixture of silver halides in a viscous medium (as a gelatin solution) forming a coating on photographic plates, film, or paper

emul·soid \i-'məl-,sȯid\ *n* (ca. 1909) **1** : a colloidal system consisting of a liquid dispersed in a liquid **2** : a lyophilic sol (as a gelatin solution)

em·sol·dal \,em-'sȯl-dᵊl\ *adj*

en \'en\ *n* (1792) **1** : the width of a piece of type half the width of an em **2** : the letter *n*

en- *also* **em-** \in *also* en; *sometimes only* in *is shown when* en *is infrequent*\ *prefix* [ME, fr. OF, fr. L *in-, im-*, fr. *in*] **1** : put into or onto ⟨*en*throne⟩ : cover with ⟨*en*shroud⟩ : go into or onto ⟨*en*plane⟩ — in verbs formed from nouns **2** : cause to be ⟨*en*slave⟩ — in verbs formed from adjectives or nouns **3** : provide with ⟨*em*power⟩ — in verbs formed from nouns **4** : so as to cover ⟨*en*wrap⟩ : thoroughly ⟨*en*tangle⟩ — in verbs formed from verbs; in all senses usu. *em-* before *b, m, p*

-en *also* **-n** *prefix* [ME, fr. L, fr. Gk, fr. *en* in — more at IN] : in : within ⟨*en*zootic⟩ — usu. *em-* before *b, m,* or *p* ⟨*em*pathy⟩

-en *comb form* [ISV; fr. *-ene*] : chemically unsaturated; *esp* : having one double bond ⟨*en*amine⟩

-en \ən\ *also* **-n** \n\ *adj suffix* [ME, fr. OE; akin to OHG *-īn* made of, *-inus* of or belonging to, Gk *-inos* made of, of or belonging to] : made of, consisting of ⟨earthen⟩ ⟨leathern⟩

-en *vt suffix* [ME *-nen*, fr. OE *-nian;* akin to OHG *-inōn* -en] **1 a** : cause to be ⟨sharpen⟩ **b** : cause to have ⟨lengthen⟩ **2 a** : come to be ⟨steepen⟩ **b** : come to have ⟨lengthen⟩

en·able \i-'nā-bəl\ *vt* **en·abled; en·abling** \-b(ə-)liŋ\ (15c) **1 a** : to provide with the means or opportunity ⟨training that ~s people to earn a living⟩ **b** : to make possible, practical, or easy **c** : to cause to operate ⟨software that ~s the keyboard⟩ **2** : to give legal power, capacity, or sanction to ⟨a law *enabling* admission of a state⟩

en·abler \i-'nā-blər, -bᵊl-ər\ *n* (1615) : one that enables another to achieve an end; *esp* : one who enables another to persist in self-destructive behavior (as substance abuse) by providing excuses or by helping that individual avoid the consequences of such behavior

en·act \i-'nakt\ *vt* (15c) **1** : to establish by legal and authoritative act; *specif* : to make (as a bill) into law **2** : ACT OUT ⟨~ a role⟩ — **en·actor** \-'nak-tər\ *n*

en·act·ment \-'nak(t)-mənt\ *n* (1817) **1** : the act of enacting : the state of being enacted **2** : something (as a law) that has been enacted

en·am·el \i-'na-məl\ *vt* **-eled** *or* **-elled; -el·ing** *or* **-el·ling** \-'nam-liŋ, -'na-mə-\ [ME, fr. MF *enamailler*, fr. *en-* + *esmail* enamel, of Gmc origin; akin to OHG *smelzan* to melt — more at SMELT] (14c) **1** : to cover, inlay, or decorate with enamel **2** : to beautify with a colorful surface **3** : to form a glossy surface on (as paper, leather, or cloth) — **enam·el·er** *n* — **enam·el·ist** \-mə-list\ *n*

²enamel *n* (15c) **1** : a usu. opaque vitreous composition applied by fusion to the surface of metal, glass, or pottery **2** : a surface or outer covering that resembles enamel **3 a** : something that is enameled **b** : ENAMELWARE **4** : a cosmetic intended to give a smooth or glossy appearance **5** : a hard calcareous substance that forms a thin layer capping the teeth — see TOOTH illustration **6** : a paint that flows out to a smooth coat when applied and that dries with a glossy appearance

enam·el·ware \i-'na-məl-,war, -,wer\ *n* (1903) : metalware (as kitchen utensils) coated with enamel

en·amine \'e-nə-,mēn, 'ē-\ *n* (1942) : an amine containing the double bond linkage C=C–N

en·am·or \i-'na-mər\ *vt* **-ored; -or·ing** \-mə-riŋ, -'nam-riŋ\ [ME *enamouren*, fr. MF *enamourer*, fr. *en-* + *amour* love — more at AMOUR] (14c) **1** : to inflame with love — usu. used in the passive with *of* **2** : FASCINATE 2b — usu. used in the passive with *of* or *with*

en·am·our *chiefly Brit var of* ENAMOR

en·an·tio·mer \i-'nan-tē-ə-mər\ *n* [Gk *enantios* + E *-mer*] (ca. 1929) : either of a pair of chemical compounds whose molecular structures have a mirror-image relationship to each other — **en·an·tio·mer·ic** \-,nan-tē-ə-'mer-ik\ *adj*

en·an·tio·morph \i-'nan-tē-ə-,mȯrf\ *n* [Gk *enantios* opposite (fr. *enanti* facing, fr. *en* in + *anti* against) + ISV *-morph* -morph] (1885) : ENANTIOMER; *also* : either of a pair of crystals (as of quartz) that are structural mirror images — **en·an·tio·mor·phic** \-,nan-tē-ə-'mȯr-fik\ *adj* — **en·an·tio·mor·phism** \-'mȯr-,fi-zəm\ *n* — **en·an·tio·mor·phous** \-'mȯr-fəs\ *adj*

ena·tion \i-'nā-shən\ *n* [L *enatus*, pp. of *enasci* to rise out of, fr. *e-* + *nasci* to be born — more at NATION] (ca. 1842) : an outgrowth from the surface of an organ ⟨a plant virus forming ~*s* on leaves⟩

en banc \ä⁰-'bäⁿk\ *adv or adj* [F, on the bench] (1863) : in full court : with full judiciary authority

en bloc \ä⁰-'bläk\ *adv or adj* [F] (1861) : as a whole : in a mass

en bro·chette \ä⁰-brō-'shet\ *adj* [F] (ca. 1909) *of food* : cooked or served on a skewer ⟨shrimp *en brochette*⟩

en·cae·nia \en-'sē-nyə\ *n pl but sing or pl in constr, often cap* [NL, fr. L, dedication festival, fr. Gk *enkainia*, fr. *en* + *kainos* new — more at RECENT] (1691) : an annual university ceremony (as at Oxford) of commemoration with recital of poems and essays and conferring of degrees

en·cage \in-'kāj, en-\ *vt* (1593) : CAGE 1

en·camp \in-'kamp, en-\ *vt* (1568) : to place or establish in a camp ~ *vi* : to set up or occupy a camp

en·camp·ment \-mənt\ *n* (1598) **1 a** : the place where a group (as a body of troops) is encamped **b** : the individuals that make up an encampment **2** : the act of encamping : the state of being encamped

en·cap·su·late \in-'kap-sə-,lāt, en-\ *vb* **-lat·ed; -lat·ing** *vt* (1876) **1** : to enclose in or as if in a capsule ⟨a pilot *encapsulated* in the cockpit⟩ **2** : EPITOMIZE, SUMMARIZE ⟨~ an era in an aphorism⟩ ~ *vi* : to become encapsulated — **en·cap·su·la·tion** \-,kap-sə-'lā-shən\ *n*

en·cap·su·lat·ed *adj* (1894) **1** : surrounded by a gelatinous or membranous envelope ⟨~ water bacteria⟩ **2** : CONDENSED

en·cap·sule \in-'kap-səl, -(,)sül, en-\ *vt* **-suled; -sul·ing** (1877) : ENCAPSULATE

en·case \in-'kās, en-\ *vt* (1633) : to enclose in or as if in a case

en·case·ment \in-'kā-smənt, en-\ *n* (1741) : the act or process of encasing : the state of being encased; *also* : CASE, COVERING

en·cash \in-'kash, en-\ *vt* (1861) *Brit* : CASH — **en·cash·able** \-'ka-shə-bəl\ *adj, chiefly Brit* — **en·cash·ment** \-mənt\ *n, chiefly Brit*

en·caus·tic \in-'kȯ-stik\ *n* [*encaustic*, adj., fr. L *encaustus*, fr. Gk *enkaustikos*, fr. *enkaiein* to burn in, fr. *en-* + *kaiein* to burn] (1601) **1** : a paint made from pigment mixed with melted beeswax and resin and after application fixed by heat **2** : the method involving the use of encaustic; *also* : a work produced by this method — **encaustic** *adj*

-ence \ən(t)s, ⁿn(t)s\ *n suffix* [ME, fr. OF, fr. L *-entia*, fr. *-ent-, -ens*, prp. ending + *-ia* ²-y] **1** : action or process ⟨emergen*ce*⟩ : instance of an action or process ⟨referen*ce*⟩ **2** : quality or state ⟨despondenc*e*⟩

¹en·ceinte \ä⁰(n)-'sant\ *adj* [MF, perh. fr. (assumed) VL *incenta*, alter. of L *incient-, inciens* being with young, modif. of Gk *enkyos* pregnant, fr. *en-* + *kyein* to be pregnant — more at CYME] (1599) : PREGNANT 3

²enceinte *n* [F, fr. OF, enclosing wall, fr. *enceindre* to surround, fr. L *incingere*, fr. *in-* + *cingere* to gird — more at CINCTURE] (ca. 1708) : a line of fortification enclosing a castle or town; *also* : the area so enclosed

encephal- *or* **encephalo-** *comb form* [F *encéphal-*, fr. Gk *enkephal-*, fr. *enkephalos*, fr. *en-* + *kephalē* head — more at CEPHALIC] : brain ⟨*encephal*itis⟩ ⟨*encephalo*myocarditis⟩

en·ceph·a·li·tis \in-,se-fə-'lī-təs\ *n, pl* **-lit·i·des** \-'li-tə-,dēz\ (1843) : inflammation of the brain — **en·ceph·a·lit·ic** \-'li-tik\ *adj*

en·ceph·a·li·to·gen·ic \-,lī-tə-'je-nik\ *adj* (1923) : tending to cause encephalitis ⟨an ~ virus⟩ — **en·ceph·a·li·to·gen** \-'lī-tə-jən, -,jen\ *n*

en·ceph·a·lo·gram \in-'se-fə-lə-,gram\ *n* (1928) : an X-ray picture of the brain made by encephalography

en·ceph·a·lo·graph \-,graf\ *n* (1928) **1** : ENCEPHALOGRAM **2** : ELECTROENCEPHALOGRAPH

en·ceph·a·log·ra·phy \in-,se-fə-'lä-grə-fē\ *n* (1922) : roentgenography of the brain after the cerebrospinal fluid has been replaced by a gas (as air)

en·ceph·a·lo·my·eli·tis \in-,se-fə-lō-,mī-ə-'lī-təs\ *n, pl* **-elit·i·des** \-ə-'li-tə-,dēz\ [NL] (1908) : concurrent inflammation of the brain and spinal cord; *specif* : any of several diseases of horses caused by viruses (genus *Alphavirus* of the family Togaviridae)

en·ceph·a·lo·myo·car·di·tis \-,mī-ə-kär-'dī-təs\ *n* [NL] (1947) : an acute febrile disease caused by a picornavirus (genus *Cardiovirus*) and

Introduction and Regulatory Perspective

Ajaz S. Hussain, Ph.D.
Food and Drug Administration

Industrial Perspective on PAT

Sonja Sekulik, *Invited*
Pfizer, Inc.

Academic Perspective on PAT

G.K. Raju, Ph.D.
Massachusetts Institute of Technology

10:20 am – 10:50 am

Break/Exhibits/Posters

12:00 pm – 2:00 pm

Lunch/Exhibits/Posters

Complimentary to all attendees

2:00 pm – 5:00 pm

Solids Processing Track:
Use of Artificial Intelligence From Formulation and Process Development

Symposium

With precise knowledge of the active ingredients, a knowledge-based Formulation and Process Expert System can be helpful to the scientist in selecting suitable excipients using information accumulated in the database. Another case where such an expert system could facilitate formulation studies is in the determination of the optimum manufacturing conditions. The presentations in this proposed symposium will address the recent advances in the use of artificial intelligence in the areas of pre-formulation, formulation and process development, troubleshooting and regulatory affairs.

Moderator

Metin Çelik, Ph.D.
PTI, Inc.

Use of an AI in Formulation and Process Development and FDA Inspection Preparations

Metin Çelik, Ph.D.
PTI, Inc.

Use of Expert Systems in Film Coating Troubleshooting

Stuart C. Porter, Ph.D.
Pharmaceutical Technologies International

Use of Artificial Expert Manager in Technology Transfer

Hashim Ahmed, Ph.D.
Hoffman-La Roche, Inc.

3:20 pm – 4:00 pm

Break/Posters

2:00 pm – 5:00 pm

Process Analytical Technologies Track:
Applications of Process Analytical Technologies in Development and Manufacture of Pharmaceutical Dosage Forms

Symposium

After the introduction to PAT provided by the previous session, this session will focus on three key technologies that have been investigated. Light-induced fluorescence, near IR and Raman spectroscopy have been investigated for their use in measurement and control during processing.

Moderators
Chetan P. Pujara, Ph.D.
Abbott Laboratories

Roger E. Williams
Bristol-Myers Squibb Company

Light-Induced Fluorescence in Development and Manufacture of Pharmaceutical Dosage Forms

C.K. Lai, Ph.D.
Massachusetts Institute of Technology

Near IR in Development and Manufacture of Pharmaceutical Dosage Forms

Kenneth R. Morris, Ph.D., *Invited*
Purdue University

Laser Induced Breakdown Spectrascopy (LIBS) in Development and Manufacturing of Pharmaceutical Dosage Forms

Mark Mowery
Merck Research Laboratories

3:20 pm – 4:00 pm

Break/Posters

5:00 pm

Adjournment

2:00 pm – 5:00 pm

Protein Processing Track: Issues in Protein Microencapsulation

Symposium

This session deals with issues important in the microencapsulation process and stability of encapsulated proteins. Various methods to improve stability of microencapsulated proteins will be described, and utilization of *in vivo* (pharmacokinetic and pharmacodynamic) data to verify the encapsulation process will be discussed. In addition, alternative methods for making microcapsules will be introduced. This session will provide cutting-edge information on microencapsulation processes and microencapsulated proteins.

Moderator
Kinam Park, Ph.D.
Purdue University

PLGA Microspheres Containing Chemically Modified Protein

Diane J. Burgess, Ph.D.
University of Connecticut

Stability of Proteins Encapsulated in PLGA Delivery Systems

Steven P. Schwendeman, Ph.D.
The University of Michigan

Novel Methods of Making Microcapsules Based on the Solvent Exchange Method

Kinam Park, Ph.D.
Purdue University

3:20 pm – 4:00 pm

Break/Posters

Friday, June 20

8:30 am – 5:30 pm

Registration

9:00 am – 12:00 pm

Solids Processing Track: Supercritical Fluid for Pharmaceutical Processes

Symposium

A supercritical fluid is a substance above its critical temperature and critical pressure. It has both gas and liquid-like properties. This dual nature allows for its use in applications where neither a gas nor a liquid are adequate. Supercritical CO^2 is currently used in pharmaceutical processing for extraction of impurities and excipients from drug substances and formulations, for extraction of synthetic intermediates, and for effecting changes in drug substance particle size and crystal morphology. This session will highlight recent applications in the areas of processing of pharmaceutical powders, formation of drug microparticles and nanoparticles, and extraction of impurities and processing aids from pharmaceutical formulations using supercritical CO^2.

Moderator
Said Saim, Ph.D.
Boehringer Ingelheim Pharmaceuticals, Inc.

Pharmaceutical Powder Processing With Supercritical Fluids

Stephen T. Horhota, Ph.D.
Boehringer Ingelheim Pharmaceuticals, Inc.

Particle Formation With Supercritical Fluids

Bala Subramanian, Ph.D.
University of Kansas

Supercritical Fluid Extraction of Impurities From Drug Substances and Products

Said Saim, Ph.D.
Boehringer Ingelheim Pharmaceuticals, Inc.

10:20 am – 10:50 am

Break/Exhibits/Posters

9:00 am – 12:00 pm

Process Analytical Technologies Track: Processing Analytical Technologies – Overview and Perspectives

Symposium

In-process measurement and control are being discussed as ways to improve manufacturing efficiency and product quality. Process Analytical Technology (PAT) consists in large part of in-process measurement and control. This session will provide an introduction and the viewpoints of three key sectors in pharmaceutical manufacturing.

Moderators
Chetan P. Pujara, Ph.D.
Abbott Laboratories

Roger E. Williams
Bristol-Myers Squibb Company

eliminated, even when large quantities of the drug are not available. Such is the focus of this symposium.

Moderator
Michael J. Pikal, Ph.D.
University of Connecticut

Control of Ice Nucleation During Freeze Drying

Jim A. Searles, Ph.D.
Eli Lilly & Company

Heat and Mass Transfer Issues in Scaling-Up Freeze-Drying Processes

Michael J. Pikal, Ph.D.
University of Connecticut

Designing of Appropriate Placebos for Cost-Saving Scaling-Up

Evgenyi Y. Shalaev, Ph.D.
Pfizer, Inc.

10:20 am – 10:50 am

Break/Posters

12:00 pm – 2:00 pm

Lunch/Posters
Complimentary to all attendees

2:00 pm – 5:00 pm

Solids Processing Track: Solvent-Free Coating Technologies

Symposium
This session will discuss principles and application of the various solvent-free coating technologies. The issues regarding selection of equipment, process conditions and formulation design will be addressed. *In vitro* characterization techniques to assess the properties of coating and to evaluate the performance of the coated dosage forms are also planned for discussion.

Moderator
Jean Z.Y. Wang, Ph.D.
Schering-Plough Research Institute

Hot Melt Coating – Equipment and Process

David M. Jones
Glatt Air Techniques, Inc., *Invited*

Principle and Application of Dry Powder Deposition Coating Technology

Stuart C. Porter, Ph.D.
Phoqus, Inc.

Photocurable Coating: An Overview and Case Study

Robin H. Bogner, Ph.D.
University of Connecticut

3:20 pm – 4:00 pm

Break/Posters

2:00 pm – 5:00 pm

Processing of Poorly Water-Soluble Drugs Track: Scale-Up of Drug Delivery Systems for Poorly Soluble Compounds

Symposium
Increasing numbers of new compounds with poor solubility come into development each year. The development scientist is challenged to find ways to improve solubility in order to develop formulations with reasonable bioavailability. Formulations using nanosystem, solid dispersion or microemulsion techniques have been successful in improving the bioavailability of poorly soluble compounds. This symposium will focus on the use of these techniques in formulation development, presenting several cases including discussion of the scale-up considerations.

Moderator
Colleen E. Ruegger, Ph.D.
Novartis Pharmaceuticals

Twin Screw Hot Melt Extrusion Processing

Matthew J. Mollan, Jr., Ph.D.
Pfizer, Inc.

Formulation and Process Approaches for Oral Nanocrystal Drug Delivery Systems

Stephen B. Ruddy, Ph.D.
élan Drug Delivery, Inc.

Challenges in the Development of Microemulsion Systems for Poorly Soluble Compounds

Angelika Mann, Ph.D.
Novartis Pharma AG

3:20 pm – 4:00 pm

Break/Posters

Wednesday, June 18

5:00 pm – 7:00 pm

Registration

Thursday, June 19

8:00 am – 5:00 pm

Registration

9:00 am – 12:00 pm

Solids Processing Track: Recent Advances in Roller Compaction

Symposium

Dry granulation with roller compactors is a quick and efficient method of producing free flowing granulations. Dry granulation does not require the use of granulation liquid, thus making it well suited for water, heat and solvent sensitive active ingredients. Due to these inherent advantages and improvements in machine designs, roller compaction has received increasing attention in recent years. Also, roller compaction equipment is capital and resource efficient compared to conventional wet granulation installations for similar throughputs. The latest developments in equipment design and formulation technologies will be discussed.

Moderator
Hamid Rezaei, Ph.D.
AstraZeneca Pharmaceuticals LP

Instrumentation and Key Design Benefits of Pharmaceutical Roller Compactors

Ronald W. Miller, Ph.D.
Bristol-Myers Squibb Company

Experimental Studies and Modeling of Roller Compaction

John C. Cunningham, Ph.D.
Merck & Company

Formulation and Scale-Up Considerations in Developing Controlled Release Matrix Dosage Forms Using Roller Compaction

Paul J. Sheskey, R.Ph.
The Dow Chemical Company

10:20 am – 10:50 am

Break/Posters

9:00 am – 12:00 pm

Processing of Poorly Water-Soluble Drugs Track: Amorphization by Grinding

Symposium

A combination of impact and attrition during grinding can bring about changes in polymorphs and hydrates of a drug and can induce amorphization as well. Amorphization of poorly water-soluble drugs increases their dissolution, which can lead to an enhancement in their bioavailability. Conversion to the amorphous state of a drug is thus desirable. However, reversion from the amorphous to the lower energy crystalline state is often observed. This session will review the basics of amorphization and discuss two case studies.

Moderator
Manish K. Gupta, Ph.D.
GlaxoSmithKline, Inc.

Assessment of Amorphization and Stabilization

Kieran J. Crowley, Ph.D.
AnorMED, Inc.

Amorphization in Physical Mixtures With a Carrier

Larry L. Augsburger, Ph.D.
University of Maryland

Formation of Physically Stable Amorphous Drugs by Co-Grinding

Robin H. Bogner, Ph.D.
University of Connecticut

10:20 am – 10:50 am

Break/Posters

9:00 am – 12:00 pm

Protein Processing Track: Scale-Up Issues in Freeze Drying

Symposium

One may argue that scale-up problems in freeze-drying are less severe than in most batch processes because the basic unit, product in a vial, is the same in both the laboratory and in manufacturing. However, it is still true that the development team may face unfortunate surprises when attempting to scale-up the freeze drying process, normally from differences in ice-nucleation behavior and/or heat and mass transfer capabilities of the dryers. It is our thesis that, with some knowledge and appropriate experiments, most of the scale-up problems may be

Goals and Objectives

This conference focuses on areas of interest to those in pharmaceutical development. Mid-level and junior scientists and graduate students are encouraged to attend and network with academic, industrial and regulatory scientists present.

Conference Objectives

- Gain knowledge on a broad range of pharmaceutical technologies
- Provide a forum for pharmaceutical scientists of all levels and students to learn about and exchange ideas on pharmaceutical processing

Conference Topics

- Industrial, academic and regulatory perspectives on Process Analytical Technologies
- Applications of Process Analytical Technologies
- Presentations by academic and industrial scientists on issues of solids modifications
- Updates on excipient functionality and harmonization
- Presentations on artificial intelligence and expert systems in formulation studies
- Presentations by academic and industrial scientists on processing of proteins and microen capsulation

Conference Highlights

- Exhibit Hall
- Career Center
- Poster sessions
- Poster and travel awards
- Online abstract submissions
- Sponsorship opportunities

Planning Committee

Chair
Robin H. Bogner, Ph.D., University of Connecticut

Vice Chair
Colleen E. Ruegger, Novartis Pharmaceuticals

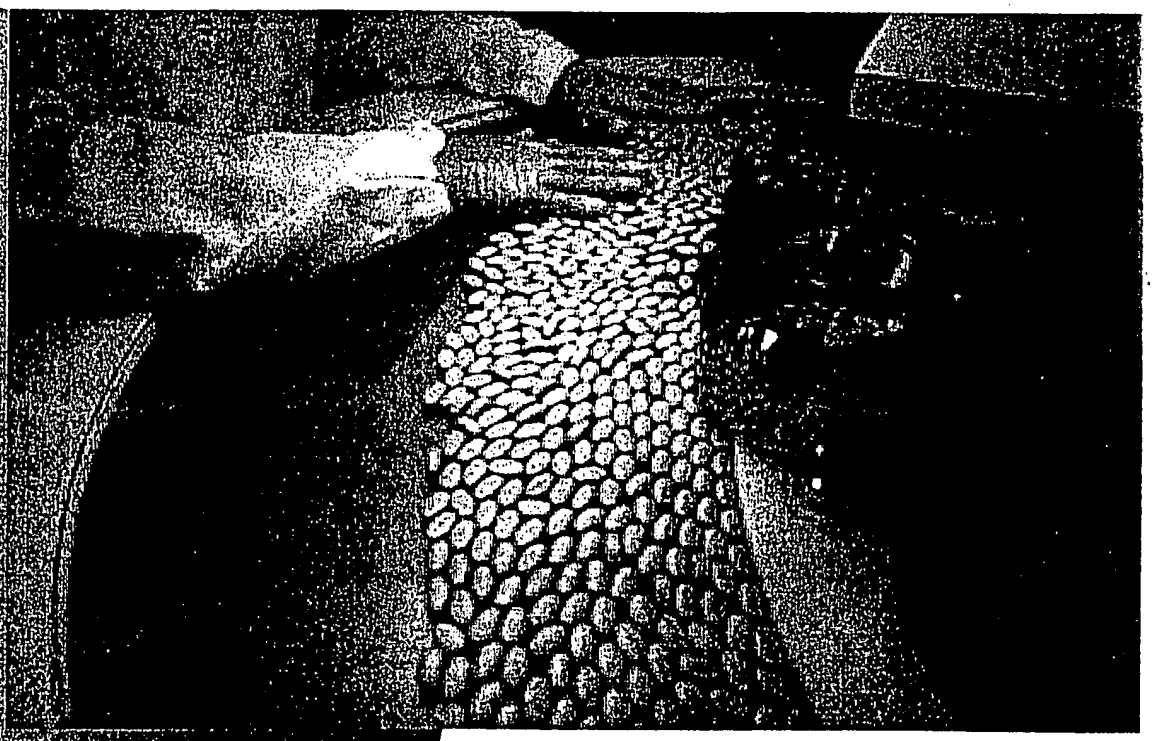
Contributed Papers Chair
Hoshang Unvala, Bayer Corporation

Exhibits Chair
Chuck Bass, Dow Chemical

Continuing Education
Melvin H. Weinswig, Ph.D., University of Wisconsin-Madison

AAPS **CONFERENCE**

Advances in Pharmaceutical Processing



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